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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/800,350	03/12/2004	Valery Krasnoperov	VASG-P01-002	2293

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EXAMINER

AEDER, SEAN E

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1642

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/800,350	Applicant(s) KRASNOPEROV ET AL.	
	Examiner SEAN E. AEDER	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 March 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26-29,32-34,38-56 and 63-68 is/are pending in the application.
- 4a) Of the above claim(s) 38-56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26-29,32-34 and 63-68 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>3/19/10</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/19/10 has been entered.

Claims 26-29, 32-34, 38-56, and 63-68 are pending.

Claims 38-56 have been withdrawn.

Claims 26-29, 32-34, and 63-68 are currently under consideration.

Response to Arguments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 26-29, 32-34, 63, and 65-68 remain rejected under 35 U.S.C. 103(a), as being unpatentable over Stephenson et al (BMC Molecular Biology, 12/21/01, 2(15): 1-9) in view of Flanagan et al (WO 96/26958; 9/6/96) and Genentech (WO 00/30673;

6/2/00), for the reasons stated in the Office Action of 10/7/08, for the reasons stated in the Office Action of 3/9/09, and for the reasons set-forth below.

Claim 26 is drawn to a monoclonal antibody which binds to an extracellular domain of an EphB4 protein and promotes apoptosis in a tumor cell, wherein the antibody is selected from bispecific, single-chain, chimeric, human, syngeneic, and humanized antibodies. Claim 27 is drawn to the antibody of claim 26, wherein the antibody inhibits the interaction between Ephrin B2 and EphB4. Claim 28 is drawn to the antibody of claim 26 wherein the antibody inhibits clustering of EphB4. Claim 29 is drawn to the antibody of claim 26, wherein the antibody inhibits phosphorylation of EphB4. Claim 32 is drawn to a pharmaceutical composition comprising the antibody of claim 26, and a pharmaceutically acceptable carrier. Claim 33 is drawn to a cosmetic composition comprising the antibody of claim 26 and a pharmaceutically acceptable carrier. Claim 34 is drawn to a diagnostic kit comprising the antibody of claim 26 and a carrier. Claim 63 is drawn to a cell expressing the antibody of claim 26. Claim 65 is drawn to the antibody of claim 26 further comprising a label attached thereto. Claim 66 is drawn to the antibody of claim 65 wherein the label is selected from a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Claim 67 is drawn to the antibody of claim 26, wherein the antibody inhibits angiogenesis. Claim 68 is drawn to the antibody of claim 26 wherein the antibody promotes tumor regression.

Stephenson et al teaches a polyclonal antibody and antibody kit available from Santa Cruz Biotechnology Inc (page 8 left column), EphB4 (H-200). As evidenced by Santa Cruz Biotechnology Inc datasheet for EphB4 (H-200), EphB4 (H-200) was raised

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against amino acids 201-400 mapping within the extracellular domain of human EphB4. Further, the datasheet states that the antibody is provided in a kit comprising a composition comprising the pharmaceutically acceptable carrier PBS. Further, Stephenson et al teaches that EphB4 protein is expressed on colon cancer tissues and either not at all, or in only low levels, in normal tissue (see Figure 4, in particular). Stephenson further teaches that therapies targeting EphB4 protein could be used in anticancer treatments (see page 2 left column, in particular). Due to the expression pattern of EphB4 protein, one of skill in the art would recognize that antibodies against EphB4 protein would also be used in methods of diagnosing colon cancer.

Stephenson does not specifically teach: monoclonal antibodies that specifically bind to an extracellular domain of EphB4 that promote apoptosis in a tumor cell that are selected from bispecific, single-chain, chimeric, human, syngeneic, and humanized antibodies; wherein the antibody inhibits the interaction between Ephrin B2 and EphB4; wherein the antibody inhibits clustering of EphB4; wherein the antibody inhibits phosphorylation of EphB4; said antibodies in a composition comprising a pharmaceutical carrier; cells expressing said antibodies; said antibodies further comprising a label such as a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor; wherein said antibodies inhibit angiogenesis; or wherein the antibodies promote tumor regression. However, these deficiencies are made up in the teachings of Flanagan et al and Genentech et al.

Flanagan et al members of the Eph receptor family play a role in growth regulation, differentiation, and oncogenesis (lines 19-23 on page 2, in particular).

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Flanagan et al further teaches labeled antibodies wherein the label is an enzyme, a radioactive substance, a chromophore, or a fluorochrome (lines 1-5 on page 20, in particular). Flanagan et al further teaches therapeutic antibodies that inhibit binding of ligands to Eph receptors (lines 7-19 on page 20, in particular).

Genentech teaches inhibiting angiogenesis and treating cancer in a mammal by administering an Eph receptor antagonist (pages 2-3, in particular). Genentech further identifies EphB4 as an Eph receptor and Ephrin B2 as a ligand for EphB4 (lines 30-32 on page 2, in particular). Genentech further teaches said antagonist as an antibody (page 6, in particular). Genentech further teaches said antagonist antagonizes the interaction between an Eph receptor and an Eph ligand, prevents or reduces tyrosine phosphorylation of Eph receptor, prevents or reduces angiogenesis, and eradicates or reduces tumor size (page 11, in particular). Genentech further teaches antibodies as monoclonal and bispecific, chimeric, and humanized (lines 26-29 on page 7 and lines 6-27 on page 8, in particular). Genentech further teaches cells expressing said antibodies and animals expressing said antibodies (line 2 on page 8, in particular). Genentech further teaches said antibodies in pharmaceutically acceptable carriers (lines 36-40 on page 22, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Stephenson et al with those of Flanagan et al and Genentech to produce monoclonal and bispecific, chimeric, and humanized antibodies that specifically bind the extracellular domain of EphrinB4 and are labeled with a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor,

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wherein said antibodies antagonize the interaction between EphrinB4 and Ephrin B2, prevent and reduce tyrosine phosphorylation of EphrinB4, prevent and reduce angiogenesis, and eradicate and reduce tumor size in order to diagnose and treat colon cancer because Stephenson et al teaches that targeting EphB4 protein is a means of treating cancer, antibodies against EphB4 protein would be used to diagnose colon cancer in view of the teachings of Stephenson et al, and EphB4 antagonist antibodies identified by an ability to bind the extracellular domain of EphrinB4 and that are labeled with a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor, wherein said antibodies antagonize the interaction between EphrinB4 and Ephrin B2, prevent and reduce tyrosine phosphorylation of EphrinB4, prevent and reduce angiogenesis, and eradicate and reduce tumor size would be therapeutically and diagnostically beneficial to humans with colon cancer. Further, one would be motivated to produce cells expressing said antibodies, by means taught by Genentech et al, in order to generate said antibodies. Further, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the teachings of Stephenson et al with those of Flanagan et al and Genentech to produce compositions comprising a pharmaceutical carrier and monoclonal and bispecific, chimeric, and humanized antibodies that specifically bind the extracellular domain of EphrinB4 and are labeled with a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor, wherein said antibodies antagonize the interaction between EphrinB4 and Ephrin B2, prevent and reduce tyrosine phosphorylation of EphrinB4, prevent and reduce angiogenesis, and eradicate and reduce tumor size in

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order to diagnose and treat colon cancer because Stephenson teaches that targeting EphB4 protein is a means of treating cancer, antibodies against EphB4 protein would diagnose colon cancer and EphB4 antagonist antibodies identified by an ability to bind the extracellular domain of EphrinB4 and that are labeled with a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor, wherein said antibodies antagonize the interaction between EphrinB4 and Ephrin B2, prevent and reduce tyrosine phosphorylation of EphrinB4, prevent and reduce angiogenesis, and eradicate and reduce tumor size would be therapeutically and diagnostically beneficial to humans with colon cancer. Further, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the teachings of Stephenson et al with those of Flanagan et al and Genentech to produce cells expressing said antibodies, in order to generate said antibodies because Genentech teaches the means required to produce said antibodies. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Further, one of skill in the art would recognize that the antibodies taught by the combined teachings above would inhibit clustering of EphB4 and promote apoptosis, as such effects would be found in the antibodies taught by the combined teachings that would sterically hinder clustering and eradicate and reduce tumor size by apoptosis. Further, *as evidenced by* Xi et al (Clinical Cancer Research, June 2005, 11(12):4305-4315), EphB4 normally phosphorylates proteins such as Akt that are known to promote tumor cell survival (page 4314, in particular). Therefore, disruption of EphB4

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phosphorylation by the antibodies produced by the combined teachings above would lead to a reduction in tumor cell survival and a shift towards apoptosis, a result obtained when siRNA reduces the expression of EphB4 in cultured cells (Figure 4, in particular). Absent a showing otherwise, the antibodies taught by the combined teachings above would inhibit clustering of EphB4 and promote apoptosis. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the antibodies of the prior art do not possess the same characteristics as the claimed antibodies. In the absence of evidence to the contrary, the burden is on Applicant to prove that the claimed antibodies are different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F .2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2nd 1992 (PTO Bd. Pat. App. & Int. 1989).

In the Reply of 3/19/10, Applicant correctly states that the antibodies of Stephenson et al do not promote apoptosis. Applicant correctly states that the antibodies of Flanagan et al do not bind EphB4 and promote apoptosis. Applicant correctly states that the antibodies of Genentech do not bind EphB4 and promote apoptosis. Applicant further argues that Xia et al does not support the proposition that antibodies that bind the extracellular domain of EphB4 must necessarily promote apoptosis. Applicant correctly states that siRNA mediated knock-down of EphB4 protein production, which results in apoptosis, is not biologically equivalent to an antibody binding to the extracellular domain of EphB4. Applicant further argues that because siRNA mediated knock-down of EphB4 results in reduction of Akt phosphorylation it does not follow that EphB4-binding antibodies must necessarily induce apoptosis.

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Applicant further argues that just any inhibition of EphB4-signaling does not result in apoptosis because Xia et al teaches that siRNA mediated knock-down of EphB4's ligand Ephrin B2 – which would inhibit EphB4 signaling –does not trigger apoptosis. Applicant further cites antibody No. 1 of Table 1 on page 36 of Krasnoperov et al (WO 2005/090406) and argues that triggering apoptosis is not an inherent feature of EphB4 binding antibodies.

The arguments found in the Reply of 3/19/10 have been carefully considered, but are not deemed persuasive. In regard to the arguments that Xia et al does not support the proposition that antibodies that bind the extracellular domain of EphB4 must necessarily promote apoptosis, that because siRNA mediated knock-down of EphB4 results in reduction of Akt phosphorylation it does not follow that EphB4-binding antibodies must necessarily induce apoptosis, and triggering apoptosis is not an inherent feature of EphB4 binding antibodies, the Examiner agrees that not all antibodies that bind EphB4 or the extracellular domain of EphB4 must necessarily promote apoptosis. However, the antibodies generated and selected by the combined teachings of Stephenson et al, Flanagan et al, and Genentech have particular characteristics in addition to binding the extracellular domain of EphB4. Such characteristics include: (1) an ability to antagonize the interaction between EphrinB4 and Ephrin B2; (3) an ability to prevent and reduce tyrosine phosphorylation of EphrinB4; (4) an ability to prevent and reduce angiogenesis; and (5) an ability to eradicate and reduce tumor size. Such selected antibodies would also promote apoptosis because, *as evidenced by Xi et al*, EphB4 normally phosphorylates proteins

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such as Akt that are known to promote tumor cell survival (page 4314, in particular).

Further, disruption of EphB4 phosphorylation by the antibodies produced by the combined teachings above would lead to a reduction in tumor cell survival and a shift towards apoptosis, a result obtained when siRNA reduces the expression of EphB4 in cultured cells (Figure 4, in particular). Further, the only antibody taught by Krasnoperov et al that binds the extracellular domain of EphB4, antagonizes the interaction between EphrinB4 and Ephrin B2, and inhibits angiogenesis *also* stimulates apoptosis (see Ab No. 23 of Table 1 on page 36).

In regards to the argument that just any inhibition of EphB4-signaling does not result in apoptosis because Xia et al teaches that siRNA mediated knock-down of EphB4's ligand Ephrin B2 – which would inhibit EphB4 signaling –does not trigger apoptosis, Xia et al have not demonstrated that siRNA mediated knock-down of EphB4's ligand Ephrin B2 inhibits EphB4 signaling in vivo or in the cells cultured with serum. Further, the combined teachings render obvious particular inhibition of EphB4 and not "just any inhibition" of EphB4 signaling. The antibodies generated and selected by the combined teachings of Stephenson et al, Flanagan et al, and Genentech would bind the extracellular domain of EphB4 and exhibit (1) an ability to antagonize the interaction between EphrinB4 and Ephrin B2; (3) an ability to prevent and reduce tyrosine phosphorylation of EphrinB4; (4) an ability to prevent and reduce angiogenesis; and (5) an ability to eradicate and reduce tumor size.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Primary Examiner, Art Unit 1642